

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Role of HDL-Associated Proteins and Lipids in the Regulation of Inflammation

Roger White, Samantha Giordano and Geeta Datta

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/67141>

Abstract

Lipoproteins are complexes of lipids and proteins that carry water-insoluble cholesterol in the bloodstream. While cholesterol is required for normal cell function, hypercholesterolemia contributes to the development of cardiovascular disease (CVD). Increased low-density lipoprotein (LDL) is a major risk factor for CVD. Reduced high-density lipoprotein (HDL) levels are inversely related to CVD risk, suggesting a protective role for HDL. Several diseases, including atherosclerosis, diabetes, chronic kidney disease and rheumatoid arthritis, have been identified where HDL levels are decreased or function is compromised. HDLs are spherical particles with a hydrophobic core of cholesteryl esters surrounded by a monolayer of phospholipids, proteins and unesterified cholesterol. Apolipoprotein (apo) A-I, the major protein component of HDL, plays an important role in the assembly and function of HDL. One of the major functions of HDL is to mediate cellular cholesterol efflux and the transfer of cholesterol from extrahepatic tissues to the liver for excretion into the bile. In addition to regulating cholesterol metabolism, HDL also exhibits antioxidative, antithrombotic and anti-inflammatory properties. Under certain conditions, however, HDL may undergo biochemical modification resulting in the formation of a particle with pro-inflammatory properties. This review will focus on the variable properties of HDL under normal physiological conditions and in the context of inflammation.

Keywords: HDL, inflammation, lipid composition, protein composition, function, macrophage mitochondria

1. Introduction

Hypercholesterolemia is an important determinant of cardiovascular disease (CVD), the leading cause of death globally [1]. Cholesterol, among other lipids, is carried in the bloodstream

from the liver to different parts of the body by lipoproteins, complex particles composed of lipids and proteins. There are four major lipoproteins that can be classified on the basis of their density: chylomicrons, very low-density lipoprotein (VLDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) [2]. Chylomicrons, VLDL and LDL are larger particles with densities ranging from 0.95 to 1.063 g/ml. HDL is a mixture of spherical particles ranging in size from 7 to 12 nm in diameter and 1.063–1.21 g/ml in density. Epidemiological studies have established an inverse relationship between HDL cholesterol and CVD risk [3, 4]. Thus, a reduction in plasma HDL levels represents an important risk factor for CVD. Results of clinical trials demonstrate that lowering LDL levels reduces CVD risk [5, 6]. Evidence supporting a role for elevated HDL in reducing CVD risk, however, is still forthcoming. Clinical trials have shown that torcetrapib, dalcetrapib and extended-release niacin significantly increase circulating HDL levels; however, this was not associated with improved outcomes [7–9]. On the other hand, raising plasma HDL by infusion or overexpression of apoA-I in murine models was shown to reduce atherogenic lesion progression [10]. One hypothesis to explain this disparity proposes that the “quality” or functional status of HDL may be a better indicator of CVD risk than plasma levels of HDL per se [11]. This review will focus on the structure-function relationship of HDL and how it influences responses to the lipoprotein in the context of inflammation.

HDL particles have a neutral core of cholesteryl ester and triglycerides (TG) surrounded by a monolayer of phospholipids, free cholesterol (FC) and protein. ApoA-I is the major protein associated with HDL particles and is synthesized in the liver and small intestine. Phospholipids and cholesterol are transferred to apoA-I by a process mediated by the ATP-binding cassette transporter type 1 (ABCA1) [12, 13] resulting in the formation of a lipid poor, dense particle called pre β -HDL. This particle plays an important role in reverse cholesterol transport, a process by which cholesterol is removed from cells. Although these particles have been predominantly studied under in vitro conditions, little information is available regarding the presence or functional significance of pre β -HDL in vivo [14]. HDL isolated from plasma by sequential ultracentrifugation yields two major subpopulations: HDL2, a large, light, lipid-rich particle (d1.063–1.125 g/ml), and HDL3, a smaller, denser protein-rich particle (d1.125–1.21 g/ml). These two particles can be further subdivided into five distinct populations: HDL2b, HDL2a, HDL3a, HDL3b and HDL3c [15]. These heterogeneous particles vary in their lipid and protein composition, forming particles of varying density, charge, and antigenicity. They also possess discrete functional properties.

2. HDL structural components

The HDL lipidome: Phospholipids (PL) represent the major lipid component of HDL, constituting about 50% by weight of all the lipids [15]. Phosphatidylcholine (PC), with a carbon backbone of varying length and saturation, is the major PL species. Lysophosphatidylcholine (LPC), phosphatidylethanolamine (PE), phosphatidylinositol (PI) and plasmalogens are also present at lower, but significant, amounts (greater than 1% of total HDL lipids by weight). Other phospholipids (phosphatidylglycerol (PG), phosphatidylserine (PS), phosphatidic acid (PA) and cardiolipin) constitute less than 1% of total HDL lipids by weight.

Sphingolipids are also well-represented in HDL particles. Sphingomyelin (SM) accounts for 5–10% by weight of total HDL lipids [15]. SM is converted to ceramide by sphingomyelinase [16]. Ceramide constitutes 0.05% by weight of total HDL lipids. Ceraminidase converts ceramide to sphingosine. Finally, the enzyme sphingosine kinase converts sphingosine to sphingosine 1-phosphate (S1P) [16]. S1P, as well as ceramide-1-phosphate, are carried by HDL and are potent signaling molecules that regulate cell growth, survival and differentiation [17]. S1P plays an important role in the suppression of inflammation [17]. S1P binding to HDL requires its physical interaction with apo M [17, 18]. Sphingosylphosphorylcholine and lysosulfatide are additional, biologically active lysosphingolipids carried by HDL [15]. The principal lipids associated with HDL particles are summarized in **Table 1**.

Proteins	Lipids
Apolipoproteins (AI-II, A-V, C-I-IV, D, E, F, M, H, O)	Phospholipids:
CETP	PC, PE, PI, PG, PS, PA
PAF-AH	
PLTP	Sphingolipids:
LCAT	SM
PON1, PON3	Ceramides
SAA1, SAA2, SAA4	S1P
Albumin	Sphingosylphosphorylcholine
Transthyretin	Lysosulfatide
Hemoglobin	
Hemopexin	
Transferrin	
Ceruloplasmin	
Vitamin D binding protein	
Complement	

Table 1. Normal protein and lipid components of HDL.

The HDL proteome: The HDL proteome has been characterized by several groups over the past 10 years. Using mass spectroscopy, the presence of at least 85 proteins on HDL have been reported [19]. These fall into different regulatory categories: lipid metabolism, acute phase response (APR), hemostasis, immune response, metal binding, vitamin transport, proteinase inhibitor and complement regulation [19, 20]. A representative list of HDL-associated proteins is shown in **Table 1**. Among these, the lipid metabolism group is the largest and contains apoA-I as well as other apolipoproteins (**Table 1**). As mentioned above, HDL exists as multiple sub-species. The proteins, lecithin-cholesterol acyltransferase (LCAT), phospholipid transfer protein (PLTP) and cholesteryl ester transfer protein (CETP), play a major role in converting HDL from one sub-species to another. APR proteins such as apo A-IV, SAA1 and SAA2 regulate lipid metabolism and are also present along with Apo J, a protein involved in

lipid metabolism and complement regulation. Surprisingly, a variety of other proteins with diverse functions such as hemoglobin, hemopexin and transferrin (iron metabolism), ceruloplasmin (metal binding), and vitamin D binding protein (vitamin binding) are also seen. These are described in detail in the review by Shah et al. [19]. Thus, the protein and lipid cargo on HDL significantly influence particle function.

3. Functions of HDL

Reverse cholesterol transport: Under hypercholesterolemic conditions, the accumulation of cholesterol in macrophages leads to the formation of “foam cells” which contribute to atheroma formation. HDL is commonly referred to as the “good cholesterol”. The salutary effect of HDL has been attributed to its ability to transfer cholesterol from extra-hepatic tissues to the liver for metabolism and excretion into the bile, a process called reverse cholesterol transport [21]. This is believed to be a critical antiatherogenic function of HDL. Cholesterol from macrophages is transferred to lipid-poor apoA-I [22] *via* ABCA1. The cholesterol is converted to cholesterol esters by the action of LCAT present on HDL. Sequestration of cholesterol esters in the hydrophobic core of the particle is associated with the formation of spherical HDL2 and HDL3. These mature HDL particles also incorporate cholesterol *via* an alternate transporter, the ATP-binding cassette transporter G1 (ABCG1) as well as the scavenger-receptor class B, type 1 (SR-BI) pathway [23]. Cholesterol-enriched HDL is subsequently removed from the circulation by hepatocytes and is excreted by the biliary pathway into bile and feces. In addition to mediating reverse cholesterol transport, HDL also possesses antioxidant, anti-inflammatory and antithrombotic properties. These pleiotropic effects of HDL play a major role in limiting inflammatory injury associated with leukocyte infiltration in the blood vessel wall.

Antioxidant properties of HDL: Chylomicrons, VLDL and LDL are apoB-containing lipoproteins which deliver cholesterol and TG to cells and are strongly implicated in atheroma formation. The response-to-retention hypothesis postulates that [24] LDL is oxidized in the arterial wall by enzymes including myeloperoxidase (MPO), NADPH oxidase, nitric oxide synthase and lipoxygenase, resulting in the accumulation of lipid hydroperoxides (LOOH) [25]. Oxidized LDL (ox-LDL) is taken up by macrophages leading to the formation of foam cells and fatty plaques. Protein and lipid components of HDL inhibit the accumulation of LOOH in LDL and prevent the formation of ox-LDL. LOOH and phosphatidyl choline hydroperoxides (PLOOH) are transferred from LDL to HDL. This process is regulated by the lipid composition and rigidity of the HDL surface. Specifically, HDL surface rigidity is determined by the ratios of SM:PC, FC:PL and saturated to polyunsaturated fatty acids (SFA:PUFA) [26]. Zerrad-Saadi and colleagues have identified the HDL3 particle as a key mediator of LOOH transfer due its optimal surface rigidity and particle content [27].

ApoA-I is likely the major HDL protein species involved in the removal of LOOH moieties from LDL. The methionine (Met) residues 112 and 148 of apoA-I can reduce LOOHs to inactive lipid hydroxides (LOH) [28]. In addition, apoA-I removes seeding LOOH molecules from LDL [29]. In addition to apoA-I, other apolipoprotein and enzyme components of HDL, such as, apo E, apo J, apo A-II, apo L-1, apo F, apo A-IV, PON1/3, PLTP and PAF-AH, play a role in

its antioxidant function. Proteomic analyses from the Davidson laboratory [30] demonstrate that HDL3c contains all these proteins along with apo M, apo D, apo A-II, SAA1,2 and 4 and apo C-I and apo C-II. This corroborates earlier studies showing that HDL3c has more potent antioxidant activity than other HDL subspecies [31, 32]. Thus, both lipid and protein components of HDL3c contribute to its antioxidant activity. Kontush et al. [32] have hypothesized that the protein components of HDL3c form a pocket which enables the transfer of LOOH from LDL which is further reduced by the concerted action of apolipoproteins and enzymes in this pocket [26].

Anti-inflammatory properties of HDL: The role of inflammation in atherogenesis has been clearly established [33–35]. Acute and chronic inflammations are associated with monocyte adhesion/infiltration and endothelial cell activation [33–35]. HDL is known to suppress the lipopolysaccharide (LPS)-induced secretion of interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), interferon- γ (IFN- γ) and other pro-inflammatory mediators [36–38]. HDL also reduces inflammation by neutralizing endotoxin, further supporting its anti-inflammatory role [39]. Thus, HDL exerts its anti-inflammatory effect in multiple ways.

Regulation of endotoxicity: In the context of infection, Gram-negative bacteria release LPS in the circulation which binds CD14 located in membrane rafts on cell surfaces. CD14 engagement facilitates the activation of toll-like receptor 4 (TLR4) binding, resulting in the release of pro-inflammatory cytokines such as IL-6 and TNF- α . HDL is able to inhibit this initial activation step *via* binding to lipid A, a glycolipid component of LPS, thus preventing TLR4 activation. Gram-positive bacteria release lipoteichoic acid (LTA) which, similar to LPS, binds CD14 and activates pro-inflammatory signaling *via* the TLR2/6 pathway [40, 41]. HDL additionally contributes to the inactivation of LPS and LTA by disrupting membrane rafts. In this manner, HDL mediates cholesterol and phospholipid efflux which destabilizes rafts and prevents the assembly of receptor complexes for LPS and LTA [14, 40].

Regulation of macrophage function: Macrophages are a versatile group of cells that play a critical role in regulating immunity, inflammation and lipid metabolism. Macrophage phenotype and function are regulated, in large part, by their environmental milieu [42–45]. On the basis of cell morphology and function, two populations of activated macrophages have been identified [46]. The classically activated M1 macrophage is induced by LPS and Th1 cytokines such as IFN- γ , interleukin-2 (IL-2) and TNF- α [43, 44]. These cells are pro-inflammatory and secrete inflammatory mediators (TNF- α , IL-1, IL-6, IL-15, IL-18, IL-23, IFN- γ), stimulate inducible nitric oxide synthase (iNOS) and promote the formation of reactive oxygen and nitrogen species [47]. The second macrophage phenotype, the alternatively activated M2 macrophage, is induced by IL-4, IL-10, IL-13 and glucocorticoid hormones [42–45]. M2 macrophages play an important role in the resolution of inflammation by inhibiting inflammatory cytokine expression and promoting wound healing [42–45]. HDL and apo A-I have been shown to promote the formation of anti-inflammatory M2 macrophages in human monocyte-derived macrophages [48] and mice [49]. As mentioned in the previous section, HDL3 is a key mediator of reverse cholesterol transport and possesses potent antioxidant properties. Reports from several laboratories suggest that HDL-associated S1P inhibits inflammation *via* activation of the PI3-kinase/*Akt* signaling pathway [50–52]. Pretreatment of bone marrow-derived

macrophages (BMDMs) with S1P suppressed LPS-induced secretion of TNF- α , monocyte chemoattractant protein (MCP) and IL-12 [53]. Additionally, Hughes and colleagues reported that S1P enhanced the activity of Arg1 and suppressed the NF- κ B-mediated induction of iNOS [53]. These responses to S1P are associated with M2 macrophage polarization.

Regulation of mitochondrial function: The mitochondrion is a double-membraned, energy-producing organelle, which contains its own maternally inherited mitochondrial DNA [54–56]. Under normal conditions, the mitochondrial respiratory chain shuttles electrons through the respiratory complexes, consumes oxygen at Complex IV and pumps hydrogen ions from inside the mitochondria to the intermembrane space at Complexes I, III and IV. This allows ATP production to proceed at the level of Complex V (ATP synthase). Under normal conditions, oxidative phosphorylation is a tightly regulated process with heat and reactive oxygen species (ROS) being produced as byproducts.

In the presence of ox-LDL and other oxidized lipids, the mitochondrion increases the formation of ROS, which can damage the mitochondria and other organelles causing cellular dysfunction and death. HDL, by virtue of its antioxidant properties, can decrease the cellular damage caused by oxidized lipids. The HDL protein PON1 hydrolyzes cholesterol esters and phospholipids in oxidized lipoproteins [52, 57, 58] thus inhibiting mitochondrial damage in the presence of oxidized lipids [58]. Further, HDL-associated apoA-I has been implicated in electron transport chain maintenance and repair [59]. In apoA-I null mice (apoA-I^{-/-}), an increase in coronary ischemia-reperfusion injury is observed compared to wild-type mice [59] and is associated with a decrease in the content of the mitochondrial protein Coenzyme Q (CoQ) in cardiomyocytes. CoQ normally supports oxidative phosphorylation by shuttling electrons from Complex II to Complex III. Exogenous administration of CoQ to apoA-I^{-/-} mice attenuated myocardial infarct size compared to the injury response in untreated mice. These data indicate the importance of HDL, and specifically, apoA-I in preserving mitochondrial structure and function.

Potential mechanisms by which HDL preserves mitochondrial function include activation of the Reperfusion Injury Salvage Kinase (RISK) pathway and the Survivor Activating Factor Enhancement (SAFE) cascade. These are cell survival pathways which are known to prevent mitochondrial damage in models of ischemic pre- and postconditioning [60]. Activation of STAT3 is an important component of the SAFE pathway and results in the downregulation of pro-apoptotic factors Bax and Bad and upregulation of antiapoptotic factor Bcl-2 and the antioxidants manganese superoxide dismutase and metallothionein [60, 61]. Further, STAT3 is transported to the mitochondrion by the GRIM-19 chaperone where it inhibits the release of cytochrome c and reduces cell death [62–64]. In a rodent model of coronary artery occlusion, the administration of apoA-I was shown to decrease infarct size and inhibit mitochondrial morphological changes seen in the heart [60]. Further analyses showed that apoA-I increased the phosphorylation of *Akt* and glycogen synthase kinase 3 beta (GSK3 β), known mediators of the RISK and SAFE survival pathways.

The S1P component of HDL is also able to activate the RISK And SAFE pathways [51, 52, 65]. Interestingly, studies conducted in neonatal rat cardiomyocytes showed that S1P is critically required for the phosphorylation of STAT3. In contrast, STAT3 phosphorylation was

absent in cells treated with HDL that was deficient in S1P [65]. In addition, S1P stimulates the phosphorylation of the transcription factor, forkhead box O-1 (FOXO-1), which inhibits ROS formation and apoptosis in the phosphorylated form [66, 67]. These data suggest that HDL activates RISK and SAFE pathways and inhibits ROS, mitochondrial dysfunction and cell death.

Interestingly, S1P has also been shown to regulate mitochondrial Complex IV assembly and cellular respiration by interacting with mitochondrial prohibitin-2 (PBH-2) [68]. PBH-2 acts as a scaffolding protein for mitochondria and its interaction with S1P during ischemic preconditioning of cardiomyocytes is essential for cardioprotection [68–70]. These data suggest that S1P can stabilize mitochondrial complexes and inhibit ROS formation, suggesting an alternate cardioprotective mechanism of S1P action.

Recent studies have suggested that other HDL-associated apolipoproteins play a role in preserving mitochondrial structure and function. ApoJ is expressed ubiquitously and is present on small dense HDL3 particles [71–73]. It is considered to be an antioxidant due to the presence of disulfide bonds that inhibit ROS-induced injury and preserve mitochondrial function [74]. Further, apoJ has been implicated in activating *Akt* and GSK3 β and the RISK survival pathway [71]. ApoM is found in association with approximately 5% of HDL particles where it confers several cytoprotective properties that include stimulating pre β -HDL formation, facilitating reverse cholesterol transport and inhibiting LDL oxidation [75–78]. ApoM also plays an important role in the cytoprotective response to S1P by binding the sphingolipid and facilitating its incorporation into HDL particles [75, 79, 80]. It follows that overexpression of apoM in mice reduces infarct size in response to ischemia-reperfusion injury and preserves mitochondrial function by increasing the HDL content of S1P.

4. Inflammation-induced alterations in HDL structure

Changes in HDL sub-species and their function have been reported in several disease states, including atherosclerosis [4], rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) [81, 82], diabetes [83], hypertension [84] and psoriasis [85–87]. Inflammation/infection triggers an APR that causes a reduction in HDL quantity and alterations in both its lipid and protein composition. Van Lenten and colleagues [88] first reported that HDL loses its ability to inhibit LDL oxidation during the APR, demonstrating that inflammation affects the structure and function of HDL.

Lipidome alterations: The phospholipid content of HDL is altered during the APR [89]. This may be due to an increase in the activity of secretory phospholipase 2 (sPLA₂) [90, 91]. Acute phase HDL also contains lower amounts of PE and PI along with several species of LPC with different levels of saturation. An important feature of acute phase HDL is that it contains oxidized phospholipids generated by the actions of transition metal ions, free radicals and hypochlorous acid (HOCl) [92, 93]. Formation of acute phase HDL in patients with coronary heart disease is also associated with a reduction in SM content [94]. An increase in triglycerides with a decrease in cholesteryl esters is also commonly observed in acute phase HDL [89].

Proteome alterations: Several changes in HDL-associated proteins arise in response to inflammation (**Table 2**). While a reduction in apo A-I represents perhaps the most prominent change in HDL composition, data suggest that the lipoprotein content of SAA may increase up to 1000-fold [85]. Endotoxin and inflammatory cytokines (TNF- α , IL-1 β and IL-6) decrease the expression of apoA-I which leads to a decrease in circulating HDL concentration [95, 96]. In addition, an increase in the synthesis of SAA results in the displacement of apoA-I from acute phase HDL [85]. Inflammation further decreases HDL levels by inducing the upregulation of sPLA₂ which degrades phospholipid components of the lipoprotein particle [89]. Loss of LCAT activity [97, 98] reduces the cholesterol carrying capacity of HDL by preventing the formation of cholesterol esters. Finally, PON1 activity is reduced by inflammation in patients with RA, SLE and psoriasis and infections and is associated with a reduction in the antioxidant capacity of HDL [99–102].

Proteins ^a		Lipids ^b	
Increased	Decreased	Increased	Decreased
Serum Amyloid A (SAA)	Apo A-I	Triglycerides	Total lipid
Apo J	Apo A-II	FC	Phospholipids
sPLA ₂	Apo C	LPC	CE
Apo E	Apo M	FFA	SM
Ceruloplasmin	LCAT		
PAF-AH	CETP		
LBP	Transferrin		
Apo A-IV	Hepatic lipase		
Apo A-V	Paraoxanase I		

^a Adapted from Refs. [87, 96, 97, 104].
^b Adapted from Refs. [15, 89, 94].

Table 2. Inflammation-induced changes in HDL composition.

The presence of apoM in HDL particles is thought to contribute to atheroprotection [103]. LPS and inflammatory cytokines, however, attenuate apoM mRNA levels and protein expression in Hep3B cells [104]. A decrease in serum apoM is also observed in patients with sepsis and HIV infections [104]. Further, a reduction in apoM reduces the association of S1P with HDL resulting in degradation of anti-inflammatory function [103].

The association of other apolipoproteins with HDL may impair the function of the lipoprotein. ApoO is incorporated by HDL, LDL and VLDL particles [105]. Data suggest that apoO provides structural stability for mitochondria by stabilizing the inner mitochondrial membrane and cristae [105]. Other data, however, show that overexpression of apoO degrades mitochondrial protein and increases cardiac dysfunction in hypercholesterolemic mice [106]. In cardiomyocyte cultures, upregulation of apoO was associated with an increase in ROS and apoptosis compared to control cells that were apoO-deficient [106]. ApoC is an additional, exchangeable apolipoprotein associated with HDL and apoB-containing lipoproteins. In iso-

lated rat liver mitochondria, addition of the apoC-III isoform was shown to inhibit mitochondrial oxygen consumption and attenuate ATP formation [107]. Another study showed that enrichment of HDL with apoC-I stimulates cytochrome c release, caspase 3 cleavage and cell death in human aortic smooth muscle cells [108]. Finally, apoC-I enrichment of HDL is associated with a reduction in HDL-associated apoA-I, suggesting that loss of apoA-I and its cytoprotective effects is a component of apoC-I-mediated cell injury [107, 108]. Clearly, additional in vitro and in vivo studies are required to define the mechanistic role of specific apolipoprotein species in the development of inflammatory injury.

5. Functional consequences of acute phase HDL formation

Changes in HDL lipid and protein composition induced by the APR impair normal HDL function resulting in the formation of “dysfunctional” HDL.

Loss of cholesterol efflux ability: Since cholesterol efflux involves the participation of apoA-I, phospholipids, LCAT and CETP, several aspects of dysfunctional HDL inhibit normal reverse cholesterol transport. The reduction in apoA-I and increase in HDL-associated SAA impair cholesterol efflux capacity [109, 110]. The presence of SAA on HDL increases foam cell formation by facilitating the uptake of cholesterol esters by macrophages. At the level of the hepatocyte, this acute phase HDL impairs cholesterol uptake and degradation [111]. Decreased content of LCAT, PL and CETP on HDL also contribute to a loss of efflux activity as does the oxidative modification of apoA-I [112, 113].

Impairment of antioxidative activity: An increase in TG and decrease in cholesterol ester content in dysfunctional HDL leads to a change in conformation of the HDL particle. The formation of a TG-rich HDL particle induces structural changes in apoA-I and decreases its stability [114]. Additionally, an increase in SAA and loss of PON1 result in a reduced antioxidant capacity of the HDL particle.

Attenuation of anti-inflammatory activity: Dysfunctional HDL has an impaired capacity to counteract the action of LPS and inflammatory cytokines. The ability to regulate membrane raft cholesterol content is reduced and can thus enhance TLR activation in response to pro-inflammatory mediators [115]. Oxidation of apoA-I also results in a loss of functionality with respect to its ability to efflux cholesterol. The protein and lipid alterations observed (reduced apoA-I, cholesterol ester, PON1 and LCAT levels and increased TG and SAA levels) are also responsible for the attenuated anti-inflammatory activity observed with dysfunctional HDL.

6. Conclusions

HDL plays an important role in regulating atherogenesis *via* its ability to mediate reverse cholesterol transport. The ability of HDL to reduce inflammatory injury and oxidant stress has also been shown to reduce CVD risk. As discussed in this review, both protein and lipid components of the lipoprotein particle play critical roles in attenuating inflammation.

Identification of these cytoprotective HDL components has been facilitated by recent proteomic analyses. Under pathological conditions, HDL levels may be reduced and the lipoprotein may undergo biochemical and structural modification resulting in the formation of dysfunctional HDL with pro-inflammatory properties. It has been suggested that the anti-inflammatory status of HDL may be of greater predictive value for CVD risk than HDL levels per se [116, 117]. Therapeutic approaches that increase the functional properties of HDL may thus be superior to simply raising circulating HDL. Unfortunately, specific and reliable biomarkers for anti-inflammatory HDL have not been identified. Under ex vivo conditions, the quality of HDL can be assessed by studying lipoprotein effects of processes such as monocyte chemotaxis and endothelial inflammation. These assays, however, are cumbersome and time-consuming. Despite these drawbacks, there is significant interest in developing new pharmacotherapies that positively impact circulating lipoproteins. Randomized clinical trials have assessed effects of several classes of drugs on plasma cholesterol levels in patients at risk. Niacin and statins significantly lower LDL and were shown to induce modest increases in HDL [8]. Residual risk, however, may be present in patients with persistently low HDL despite a reduction in LDL. CETP inhibitors have been shown to increase HDL levels in animal models and in human subjects with low HDL [118, 119]. The ILLUMINATE trial tested effects of the CETP inhibitor torcetrapib on HDL and outcomes in high risk patients but was terminated early due to an increase in mortality due to off-target effects [7]. In ongoing studies, the antiatherogenic and anti-inflammatory effects of reconstituted HDL therapy as well as apolipoprotein mimetics are being evaluated. Recent exciting data also show that HDL serves as a carrier for functional miRNAs that suppress inflammation at the level of the endothelial cell [120]. miRNAs have also been identified that regulate HDL biogenesis [121]. These recent observations may lay the foundation for a new field of miRNA-based HDL therapeutics.

Author details

Roger White¹, Samantha Giordano¹ and Geeta Datta^{2*}

*Address all correspondence to: gdatta@uabmc.edu

¹ Department of Medicine, University of Alabama at Birmingham, USA

² Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

References

- [1] Gotto AM, Jr. Jeremiah Metzger Lecture: cholesterol, inflammation and atherosclerotic cardiovascular disease: is it all LDL? Transactions of the American Clinical and Climatological Association. 2011;122:256–89.
- [2] Lewis B. Classification of lipoproteins and lipoprotein disorders. Journal of Clinical Pathology Supplement. 1973;5:26–31.

- [3] Gordon DJ, Rifkind BM. High-density lipoprotein—the clinical implications of recent studies. *The New England Journal of Medicine*. 1989;321:1311–6.
- [4] Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. *The American Journal of Medicine*. 1977;62:707–14.
- [5] Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *The New England Journal of Medicine*. 2008;359:2195–207.
- [6] Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *The New England Journal of Medicine*. 2016;374:2021–31.
- [7] Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, et al. Effects of torcetrapib in patients at high risk for coronary events. *The New England Journal of Medicine*. 2007;357:2109–22.
- [8] Investigators A-H. HDL cholesterol levels receiving intensive statin therapy. *New England Journal of Medicine*. 2011;365:2255–67.
- [9] Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *The New England Journal of Medicine*. 2012;367:2089–99.
- [10] Plump AS, Scott CJ, Breslow JL. Human apolipoprotein A-I gene expression increases high density lipoprotein and suppresses atherosclerosis in the apolipoprotein E-deficient mouse. *Proceedings of the National Academy of Sciences of the United States of America*. 1994;91:9607–11.
- [11] Joy T, Hegele RA. Is raising HDL a futile strategy for atheroprotection? *Nature Reviews Drug discovery*. 2008;7:143–55.
- [12] Asztalos BF, de la Llera-Moya M, Dallal GE, Horvath KV, Schaefer EJ, Rothblat GH. Differential effects of HDL subpopulations on cellular ABCA1- and SR-BI-mediated cholesterol efflux. *Journal of Lipid Research*. 2005;46:2246–53.
- [13] Duong PT, Weibel GL, Lund-Katz S, Rothblat GH, Phillips MC. Characterization and properties of pre beta-HDL particles formed by ABCA1-mediated cellular lipid efflux to apoA-I. *Journal of Lipid Research*. 2008;49:1006–14.
- [14] Zhu X, Parks JS. New roles of HDL in inflammation and hematopoiesis. *Annual Review of Nutrition*. 2012;32:161–82.
- [15] Kontush A, Lhomme M, Chapman MJ. Unraveling the complexities of the HDL lipiome. *Journal of Lipid Research*. 2013;54:2950–63.
- [16] Nixon GF. Sphingolipids in inflammation: pathological implications and potential therapeutic targets. *British Journal of Pharmacology*. 2009;158:982–93.

- [17] Maceyka M, Spiegel S. Sphingolipid metabolites in inflammatory disease. *Nature*. 2014;510:58–67.
- [18] Hla T, Dannenberg AJ. Sphingolipid signaling in metabolic disorders. *Cell Metabolism*. 2012;16:420–34.
- [19] Shah AS, Tan L, Long JL, Davidson WS. Proteomic diversity of high density lipoproteins: our emerging understanding of its importance in lipid transport and beyond. *Journal of Lipid Research*. 2013;54:2575–85.
- [20] Vaisar T, Pennathur S, Green PS, Gharib SA, Hoofnagle AN, Cheung MC, et al. Shotgun proteomics implicates protease inhibition and complement activation in the antiinflammatory properties of HDL. *The Journal of Clinical Investigation*. 2007;117:746–56.
- [21] Fazio S, Linton MF. Sorting out the complexities of reverse cholesterol transport: CETP polymorphisms, HDL, and coronary disease. *The Journal of Clinical Endocrinology and Metabolism*. 2006;91:3273–5.
- [22] Du XM, Kim MJ, Hou L, Le Goff W, Chapman MJ, Van Eck M, et al. HDL particle size is a critical determinant of ABCA1-mediated macrophage cellular cholesterol export. *Circulation Research*. 2015;116:1133–42.
- [23] Rosenson RS, Brewer HB, Jr., Davidson WS, Fayad ZA, Fuster V, Goldstein J, et al. Cholesterol efflux and atheroprotection: advancing the concept of reverse cholesterol transport. *Circulation*. 2012;125:1905–19.
- [24] Williams KJ, Tabas I. The response-to-retention hypothesis of early atherogenesis. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 1995;15:551–61.
- [25] Gaut JP, Heinecke JW. Mechanisms for oxidizing low-density lipoprotein. Insights from patterns of oxidation products in the artery wall and from mouse models of atherosclerosis. *Trends in Cardiovascular Medicine*. 2001;11:103–12.
- [26] Kontush A, Chapman MJ. Antiatherogenic function of HDL particle subpopulations: focus on antioxidative activities. *Current Opinion in Lipidology*. 2010;21:312–8.
- [27] Zerrad-Saadi A, Therond P, Chantepie S, Couturier M, Rye KA, Chapman MJ, et al. HDL3-mediated inactivation of LDL-associated phospholipid hydroperoxides is determined by the redox status of apolipoprotein A-I and HDL particle surface lipid rigidity: relevance to inflammation and atherogenesis. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2009;29:2169–75.
- [28] Garner B, Waldeck AR, Witting PK, Rye KA, Stocker R. Oxidation of high density lipoproteins. II. Evidence for direct reduction of lipid hydroperoxides by methionine residues of apolipoproteins AI and AII. *The Journal of Biological Chemistry*. 1998;273:6088–95.
- [29] Navab M, Hama SY, Cooke CJ, Anantharamaiah GM, Chaddha M, Jin L, et al. Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low density lipoprotein: step 1. *Journal of Lipid Research*. 2000;41:1481–94.

- [30] Davidson WS, Silva RA, Chantepie S, Lagor WR, Chapman MJ, Kontush A. Proteomic analysis of defined HDL subpopulations reveals particle-specific protein clusters: relevance to antioxidative function. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2009;29:870–6.
- [31] Kontush A, Chantepie S, Chapman MJ. Small, dense HDL particles exert potent protection of atherogenic LDL against oxidative stress. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2003;23:1881–8.
- [32] Kontush A, de Faria EC, Chantepie S, Chapman MJ. Antioxidative activity of HDL particle subspecies is impaired in hyperalphalipoproteinemia: relevance of enzymatic and physicochemical properties. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2004;24:526–33.
- [33] Frostegard J. Immunity, atherosclerosis and cardiovascular disease. *BMC Medicine*. 2013;11:117.
- [34] Tabas I, Garcia-Cardena G, Owens GK. Recent insights into the cellular biology of atherosclerosis. *The Journal of Cell Biology*. 2015;209:13–22.
- [35] Manduteanu I, Simionescu M. Inflammation in atherosclerosis: a cause or a result of vascular disorders? *Journal of Cellular and Molecular Medicine*. 2012;16:1978–90.
- [36] Catapano AL, Pirillo A, Bonacina F, Norata GD. HDL in innate and adaptive immunity. *Cardiovascular Research*. 2014;103:372–83.
- [37] Guo L, Ai J, Zheng Z, Howatt DA, Daugherty A, Huang B, et al. High density lipoprotein protects against polymicrobe-induced sepsis in mice. *The Journal of Biological Chemistry*. 2013;288:17947–53.
- [38] Levine DM, Parker TS, Donnelly TM, Walsh A, Rubin AL. In vivo protection against endotoxin by plasma high density lipoprotein. *Proceedings of the National Academy of Sciences of the United States of America*. 1993;90:12040–4.
- [39] Morin EE, Guo L, Schwendeman A, Li XA. HDL in sepsis—risk factor and therapeutic approach. *Frontiers in Pharmacology*. 2015;6:244.
- [40] White CR, Smythies LE, Crossman DK, Palgunachari MN, Anantharamaiah GM, Datta G. Regulation of pattern recognition receptors by the apolipoprotein A-I mimetic peptide 4F. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2012;32:2631–9.
- [41] Triantafilou M, Manukyan M, Mackie A, Morath S, Hartung T, Heine H, et al. Lipoteichoic acid and toll-like receptor 2 internalization and targeting to the Golgi are lipid raft-dependent. *The Journal of Biological Chemistry*. 2004;279:40882–9.
- [42] Labonte AC, Tosello-Tramont AC, Hahn YS. The role of macrophage polarization in infectious and inflammatory diseases. *Molecules and Cells*. 2014;37:275–85.
- [43] Lawrence T, Natoli G. Transcriptional regulation of macrophage polarization: enabling diversity with identity. *Nature Reviews Immunology*. 2011;11:750–61.

- [44] Martinez FO, Sica A, Mantovani A, Locati M. Macrophage activation and polarization. *Frontiers in Bioscience: a Journal and Virtual Library*. 2008;13:453–61.
- [45] Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. *Nature Reviews Immunology*. 2008;8:958–69.
- [46] Mosser DM. The many faces of macrophage activation. *Journal of Leukocyte Biology*. 2003;73:209–12.
- [47] Porta C, Rimoldi M, Raes G, Brys L, Ghezzi P, Di Liberto D, et al. Tolerance and M2 (alternative) macrophage polarization are related processes orchestrated by p50 nuclear factor kappaB. *Proceedings of the National Academy of Sciences of the United States of America*. 2009;106:14978–83.
- [48] Smythies LE, White CR, Maheshwari A, Palgunachari MN, Anantharamaiah GM, Chaddha M, et al. Apolipoprotein A-I mimetic 4F alters the function of human monocyte-derived macrophages. *American Journal of Physiology Cell Physiology*. 2010;298:C1538–48.
- [49] Feig JE, Rong JX, Shamir R, Sanson M, Vengrenyuk Y, Liu J, et al. HDL promotes rapid atherosclerosis regression in mice and alters inflammatory properties of plaque monocyte-derived cells. *Proceedings of the National Academy of Sciences of the United States of America*. 2011;108:7166–71.
- [50] Argraves KM, Gazzolo PJ, Groh EM, Wilkerson BA, Matsuura BS, Twal WO, et al. High density lipoprotein-associated sphingosine 1-phosphate promotes endothelial barrier function. *The Journal of Biological Chemistry*. 2008;283:25074–81.
- [51] Keul P, Sattler K, Levkau B. HDL and its sphingosine-1-phosphate content in cardioprotection. *Heart Failure Reviews*. 2007;12:301–6.
- [52] Theilmeier G, Schmidt C, Herrmann J, Keul P, Schafers M, Herrgott I, et al. High-density lipoproteins and their constituent, sphingosine-1-phosphate, directly protect the heart against ischemia/reperfusion injury in vivo via the S1P3 lysophospholipid receptor. *Circulation*. 2006;114:1403–9.
- [53] Hughes JE, Srinivasan S, Lynch KR, Proia RL, Ferdek P, Hedrick CC. Sphingosine-1-phosphate induces an antiinflammatory phenotype in macrophages. *Circulation Research*. 2008;102:950–8.
- [54] Amo T, Yadava N, Oh R, Nicholls DG, Brand MD. Experimental assessment of bioenergetic differences caused by the common European mitochondrial DNA haplogroups H and T. *Gene*. 2008;411:69–76.
- [55] Fetterman JL, Zelickson BR, Johnson LW, Moellering DR, Westbrook DG, Pompilius M, et al. Mitochondrial genetic background modulates bioenergetics and susceptibility to acute cardiac volume overload. *The Biochemical Journal*. 2013;455:157–67.
- [56] Lee J, Giordano S, Zhang J. Autophagy, mitochondria and oxidative stress: cross-talk and redox signalling. *The Biochemical Journal*. 2012;441:523–40.

- [57] Garcia-Heredia A, Marsillach J, Rull A, Triguero I, Fort I, Mackness B, et al. Paraoxonase-1 inhibits oxidized low-density lipoprotein-induced metabolic alterations and apoptosis in endothelial cells: a nondirected metabolomic study. *Mediators of Inflammation*. 2013;2013:156053.
- [58] Sangle GV, Chowdhury SK, Xie X, Stelmack GL, Halayko AJ, Shen GX. Impairment of mitochondrial respiratory chain activity in aortic endothelial cells induced by glycated low-density lipoprotein. *Free Radical Biology & Medicine*. 2010;48:781–90.
- [59] Dadabayev AR, Yin G, Latchoumycandane C, McIntyre TM, Lesnefsky EJ, Penn MS. Apolipoprotein A1 regulates coenzyme Q10 absorption, mitochondrial function, and infarct size in a mouse model of myocardial infarction. *The Journal of Nutrition*. 2014;144:1030–6.
- [60] Kalakech H, Hibert P, Prunier-Mirebeau D, Tamareille S, Letournel F, Macchi L, et al. RISK and SAFE signaling pathway involvement in apolipoprotein A-I-induced cardioprotection. *PLoS One*. 2014;9:e107950.
- [61] Lecour S. Multiple protective pathways against reperfusion injury: a SAFE path without Aktion? *Journal of Molecular and Cellular Cardiology*. 2009;46:607–9.
- [62] Szczepanek K, Chen Q, Derecka M, Salloum FN, Zhang Q, Szelag M, et al. Mitochondrial-targeted signal transducer and activator of transcription 3 (STAT3) protects against ischemia-induced changes in the electron transport chain and the generation of reactive oxygen species. *The Journal of Biological Chemistry*. 2011;286:29610–20.
- [63] Tammineni P, Anugula C, Mohammed F, Anjaneyulu M, Larner AC, Sepuri NB. The import of the transcription factor STAT3 into mitochondria depends on GRIM-19, a component of the electron transport chain. *The Journal of Biological Chemistry*. 2013;288:4723–32.
- [64] Wegrzyn J, Potla R, Chwae YJ, Sepuri NB, Zhang Q, Koeck T, et al. Function of mitochondrial Stat3 in cellular respiration. *Science*. 2009;323:793–7.
- [65] Frias MA, Lecour S, James RW, Pedretti S. High density lipoprotein/sphingosine-1-phosphate-induced cardioprotection: role of STAT3 as part of the SAFE pathway. *Jak-Stat*. 2012;1:92–100.
- [66] Somers SJ, Frias M, Lacerda L, Opie LH, Lecour S. Interplay between SAFE and RISK pathways in sphingosine-1-phosphate-induced cardioprotection. *Cardiovascular Drugs and Therapy/sponsored by the International Society of Cardiovascular Pharmacotherapy*. 2012;26:227–37.
- [67] Zhang J, Honbo N, Goetzl EJ, Chatterjee K, Karliner JS, Gray MO. Signals from type 1 sphingosine 1-phosphate receptors enhance adult mouse cardiac myocyte survival during hypoxia. *American Journal of Physiology Heart and Circulatory Physiology*. 2007;293:H3150–8.
- [68] Gomez L, Paillard M, Price M, Chen Q, Teixeira G, Spiegel S, et al. A novel role for mitochondrial sphingosine-1-phosphate produced by sphingosine kinase-2 in PTP-mediated cell survival during cardioprotection. *Basic Research in Cardiology*. 2011;106:1341–53.

- [69] Merkwirth C, Langer T. Prohibitin function within mitochondria: essential roles for cell proliferation and cristae morphogenesis. *Biochimica et biophysica acta*. 2009; 1793:27–32.
- [70] Strub GM, Paillard M, Liang J, Gomez L, Allegood JC, Hait NC, et al. Sphingosine-1-phosphate produced by sphingosine kinase 2 in mitochondria interacts with prohibitin 2 to regulate complex IV assembly and respiration. *FASEB Journal*. 2011;25:600–12.
- [71] de Silva HV, Stuart WD, Duvic CR, Wetterau JR, Ray MJ, Ferguson DG, et al. A 70-kDa apolipoprotein designated ApoJ is a marker for subclasses of human plasma high density lipoproteins. *The Journal of Biological Chemistry*. 1990;265:13240–7.
- [72] Park S, Mathis KW, Lee IK. The physiological roles of apolipoprotein J/clusterin in metabolic and cardiovascular diseases. *Reviews in Endocrine & Metabolic Disorders*. 2014;15:45–53.
- [73] Trougakos IP. The molecular chaperone apolipoprotein J/clusterin as a sensor of oxidative stress: implications in therapeutic approaches—a mini-review. *Gerontology*. 2013;59:514–23.
- [74] Jun HO, Kim DH, Lee SW, Lee HS, Seo JH, Kim JH, et al. Clusterin protects H9c2 cardiomyocytes from oxidative stress-induced apoptosis via Akt/GSK-3 β signaling pathway. *Experimental & Molecular Medicine*. 2011;43:53–61.
- [75] Blaho VA, Hla T. An update on the biology of sphingosine 1-phosphate receptors. *Journal of Lipid Research*. 2014;55:1596–608.
- [76] Christoffersen C, Ahnstrom J, Axler O, Christensen EI, Dahlback B, Nielsen LB. The signal peptide anchors apolipoprotein M in plasma lipoproteins and prevents rapid clearance of apolipoprotein M from plasma. *The Journal of Biological Chemistry*. 2008;283:18765–72.
- [77] Dahlback B, Nielsen LB. Apolipoprotein M affecting lipid metabolism or just catching a ride with lipoproteins in the circulation? *Cellular and Molecular Life Sciences: CMLS*. 2009;66:559–64.
- [78] Elsoe S, Christoffersen C, Luchoomun J, Turner S, Nielsen LB. Apolipoprotein M promotes mobilization of cellular cholesterol in vivo. *Biochimica et Biophysica Acta*. 2013;1831:1287–92.
- [79] Christoffersen C, Obinata H, Kumaraswamy SB, Galvani S, Ahnstrom J, Sevvana M, et al. Endothelium-protective sphingosine-1-phosphate provided by HDL-associated apolipoprotein M. *Proceedings of the National Academy of Sciences of the United States of America*. 2011;108:9613–8.
- [80] Duan J, Dahlback B, Villoutreix BO. Proposed lipocalin fold for apolipoprotein M based on bioinformatics and site-directed mutagenesis. *FEBS Letters*. 2001;499:127–32.
- [81] Ormseth MJ, Stein CM. High-density lipoprotein function in rheumatoid arthritis. *Current Opinion in Lipidology*. 2016;27:67–75.

- [82] Hahn BH, Grossman J, Ansell BJ, Skaggs BJ, McMahon M. Altered lipoprotein metabolism in chronic inflammatory states: proinflammatory high-density lipoprotein and accelerated atherosclerosis in systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Research & Therapy*. 2008;10:213.
- [83] Van Linthout S, Spillmann F, Schultheiss HP, Tschope C. High-density lipoprotein at the interface of type 2 diabetes mellitus and cardiovascular disorders. *Current Pharmaceutical Design*. 2010;16:1504–16.
- [84] Odden MC, Tager IB, Gansevoort RT, Bakker SJ, Fried LF, Newman AB, et al. Hypertension and low HDL cholesterol were associated with reduced kidney function across the age spectrum: a collaborative study. *Annals of Epidemiology*. 2013;23:106–11.
- [85] Feingold KR, Grunfeld C. Effect of inflammation on HDL structure and function. *Current Opinion in Lipidology*. 2016;27:521–30.
- [86] Holzer M, Wolf P, Curcic S, Birner-Gruenberger R, Weger W, Inzinger M, et al. Psoriasis alters HDL composition and cholesterol efflux capacity. *Journal of Lipid Research*. 2012;53:1618–24.
- [87] Mehta NN, Gelfand JM. High-density lipoprotein cholesterol function improves after successful treatment of psoriasis: a step forward in the right direction. *The Journal of Investigative Dermatology*. 2014;134:592–5.
- [88] Van Lenten BJ, Hama SY, de Beer FC, Stafforini DM, McIntyre TM, Prescott SM, et al. Anti-inflammatory HDL becomes pro-inflammatory during the acute phase response. Loss of protective effect of HDL against LDL oxidation in aortic wall cell cocultures. *The Journal of Clinical Investigation*. 1995;96:2758–67.
- [89] Khovidhunkit W, Kim MS, Memon RA, Shigenaga JK, Moser AH, Feingold KR, et al. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. *Journal of Lipid Research*. 2004;45:1169–96.
- [90] Crowl RM, Stoller TJ, Conroy RR, Stoner CR. Induction of phospholipase A2 gene expression in human hepatoma cells by mediators of the acute phase response. *The Journal of Biological Chemistry*. 1991;266:2647–51.
- [91] Pruzanski W, Vadas P, Browning J. Secretory non-pancreatic group II phospholipase A2: role in physiologic and inflammatory processes. *Journal of Lipid Mediators*. 1993;8:161–7.
- [92] Navab M, Berliner JA, Subbanagounder G, Hama S, Lusis AJ, Castellani LW, et al. HDL and the inflammatory response induced by LDL-derived oxidized phospholipids. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2001;21:481–8.
- [93] Stocker R. Lipoprotein oxidation: mechanistic aspects, methodological approaches and clinical relevance. *Current Opinion in Lipidology*. 1994;5:422–33.
- [94] Pruzanski W, Stefanski E, de Beer FC, de Beer MC, Ravandi A, Kuksis A. Comparative analysis of lipid composition of normal and acute-phase high density lipoproteins. *Journal of Lipid Research*. 2000;41:1035–47.

- [95] Ettinger WH, Varma VK, Sorci-Thomas M, Parks JS, Sigmon RC, Smith TK, et al. Cytokines decrease apolipoprotein accumulation in medium from Hep G2 cells. *Arteriosclerosis and Thrombosis: A Journal of Vascular Biology/American Heart Association*. 1994;14:8–13.
- [96] Haas MJ, Horani M, Mreyoud A, Plummer B, Wong NC, Mooradian AD. Suppression of apolipoprotein AI gene expression in HepG2 cells by TNF alpha and IL-1beta. *Biochimica et Biophysica Acta*. 2003;1623:120–8.
- [97] Navab M, Hama-Levy S, Van Lenten BJ, Fonarow GC, Cardinez CJ, Castellani LW, et al. Mildly oxidized LDL induces an increased apolipoprotein J/paraoxonase ratio. *The Journal of Clinical Investigation*. 1997;99:2005–19.
- [98] Van Lenten BJ, Wagner AC, Nayak DP, Hama S, Navab M, Fogelman AM. High-density lipoprotein loses its anti-inflammatory properties during acute influenza a infection. *Circulation*. 2001;103:2283–8.
- [99] Draganov D, Teiber J, Watson C, Bisgaier C, Nemzek J, Remick D, et al. PON1 and oxidative stress in human sepsis and an animal model of sepsis. *Advances in Experimental Medicine and Biology*. 2010;660:89–97.
- [100] He L, Qin S, Dang L, Song G, Yao S, Yang N, et al. Psoriasis decreases the anti-oxidation and anti-inflammation properties of high-density lipoprotein. *Biochimica et Biophysica Acta*. 2014;1841:1709–15.
- [101] Isik A, Koca SS, Ustundag B, Celik H, Yildirim A. Paraonase and arylesterase levels in rheumatoid arthritis. *Clinical Rheumatology*. 2007;26:342–8.
- [102] Novak F, Vavrova L, Kodydkova J, Novak F, Sr., Hynkova M, Zak A, et al. Decreased paraonase activity in critically ill patients with sepsis. *Clinical and Experimental Medicine*. 2010;10:21–5.
- [103] Ren K, Tang ZL, Jiang Y, Tan YM, Yi GH. Apolipoprotein M. *Clinica Chimica Acta; International Journal of Clinical Chemistry*. 2015;446:21–9.
- [104] Feingold KR, Shigenaga JK, Chui LG, Moser A, Khovidhunkit W, Grunfeld C. Infection and inflammation decrease apolipoprotein M expression. *Atherosclerosis*. 2008;199:19–26.
- [105] Lamant M, Smih F, Harmancey R, Philip-Couderc P, Pathak A, Roncalli J, et al. ApoO, a novel apolipoprotein, is an original glycoprotein up-regulated by diabetes in human heart. *The Journal of Biological Chemistry*. 2006;281:36289–302.
- [106] Turkieh A, Caubere C, Barutaut M, Desmoulin F, Harmancey R, Galinier M, et al. Apolipoprotein O is mitochondrial and promotes lipotoxicity in heart. *The Journal of Clinical Investigation*. 2014;124:2277–86.
- [107] Panin LE, Shalbueva NI, Polyakov LM. Effects of apolipoproteins C on oxidative phosphorylation in rat liver mitochondria. *Bulletin of Experimental Biology and Medicine*. 2000;130:769–71.

- [108] Kolmakova A, Kwiterovich P, Virgil D, Alaupovic P, Knight-Gibson C, Martin SF, et al. Apolipoprotein C-I induces apoptosis in human aortic smooth muscle cells via recruiting neutral sphingomyelinase. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2004;24:264–9.
- [109] Banka CL, Yuan T, de Beer MC, Kindy M, Curtiss LK, de Beer FC. Serum amyloid A (SAA): influence on HDL-mediated cellular cholesterol efflux. *Journal of Lipid Research*. 1995;36:1058–65.
- [110] Kontush A, Chapman MJ. Functionally defective high-density lipoprotein: a new therapeutic target at the crossroads of dyslipidemia, inflammation, and atherosclerosis. *Pharmacological Reviews*. 2006;58:342–74.
- [111] Cai L, de Beer MC, de Beer FC, van der Westhuyzen DR. Serum amyloid A is a ligand for scavenger receptor class B type I and inhibits high density lipoprotein binding and selective lipid uptake. *The Journal of Biological Chemistry*. 2005;280:2954–61.
- [112] Shao B, Bergt C, Fu X, Green P, Voss JC, Oda MN, et al. Tyrosine 192 in apolipoprotein A-I is the major site of nitration and chlorination by myeloperoxidase, but only chlorination markedly impairs ABCA1-dependent cholesterol transport. *The Journal of Biological Chemistry*. 2005;280:5983–93.
- [113] Zheng L, Settle M, Brubaker G, Schmitt D, Hazen SL, Smith JD, et al. Localization of nitration and chlorination sites on apolipoprotein A-I catalyzed by myeloperoxidase in human atheroma and associated oxidative impairment in ABCA1-dependent cholesterol efflux from macrophages. *The Journal of Biological Chemistry*. 2005;280:38–47.
- [114] Curtiss LK, Bonnet DJ, Rye KA. The conformation of apolipoprotein A-I in high-density lipoproteins is influenced by core lipid composition and particle size: a surface plasmon resonance study. *Biochemistry*. 2000;39:5712–21.
- [115] Azzam KM, Fessler MB. Crosstalk between reverse cholesterol transport and innate immunity. *Trends in Endocrinology and Metabolism: TEM*. 2012;23:169–78.
- [116] deGoma EM, deGoma RL, Rader DJ. Beyond high-density lipoprotein cholesterol levels evaluating high-density lipoprotein function as influenced by novel therapeutic approaches. *Journal of the American College of Cardiology*. 2008;51:2199–211.
- [117] Luscher TF, Landmesser U, von Eckardstein A, Fogelman AM. High-density lipoprotein: vascular protective effects, dysfunction, and potential as therapeutic target. *Circulation Research*. 2014;114:171–82.
- [118] Brousseau ME, Schaefer EJ, Wolfe ML, Bloedon LT, Digenio AG, Clark RW, et al. Effects of an inhibitor of cholesteryl ester transfer protein on HDL cholesterol. *The New England Journal of Medicine*. 2004;350:1505–15.
- [119] Morehouse LA, Sugarman ED, Bourassa PA, Sand TM, Zimetti F, Gao F, et al. Inhibition of CETP activity by torcetrapib reduces susceptibility to diet-induced atherosclerosis in New Zealand White rabbits. *Journal of Lipid Research*. 2007;48:1263–72.

- [120] Tabet F, Vickers KC, Cuesta Torres LF, Wiese CB, Shoucri BM, Lambert G, et al. HDL-transferred microRNA-223 regulates ICAM-1 expression in endothelial cells. *Nature Communications*. 2014;5:3292.
- [121] Rayner KJ, Moore KJ. MicroRNA control of high-density lipoprotein metabolism and function. *Circulation Research*. 2014;114:183–92.

IntechOpen

IntechOpen